Human induced pluripotent stem cell-derived cardiomyocytes as an in vitro model for coxsackievirus B3-induced myocarditis and antiviral drug screening platform.

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Public Summary:
Viral myocarditis is a deadly disease affecting both children and adults and causes significant morbidity and mortality. The diagnosis of this disease is often difficult and there is no effective treatment to prevent the down stream sequelae of viral myocarditis including heart failure from heart enlargement and rhythm disorder that causes sudden death. We set out in this study to develop a way to study how the virus (coxsackievirus B3) that is the most common virus responsible for this disease is able to infect human heart muscle cells and to determine whether we can develop an assay that would allow us to test candidate drugs that may be able to reduce/minimize/eliminate the ability of the virus to infect and to grow inside human heart muscle cells. We used human induced pluripotent stem cells (iPSCs) and generated heart muscle cells from these stem cells and add the virus to these cells to see what effects do the viruses have on cell's survival and growth. We also tested the effect of a few candidate drugs that have been suggested to prevent infection of this virus, for example, interferon-beta, on the ability of the virus to grow and expand. We show that the human iPSC derived heart muscle cells express the receptor for the coxsackievirus B3 and are susceptible to being infect by them. This process simulates what does on when humans are being infected with the virus. We then down that treating of human iPSC cardiomyocytes with interferon-beta and other candidate drugs are able to reduce the level of infection by these viruses. Our study will now provide a way for drug companies and scientists to measure the ability of their lead drug candidate to protect against viral myocarditis.

Scientific Abstract:
RATIONALE: Viral myocarditis is a life-threatening illness that may lead to heart failure or cardiac arrhythmias. A major causative agent for viral myocarditis is the B3 strain of coxsackievirus, a positive-sense RNA enterovirus. However, human cardiac tissues are difficult to procure in sufficient enough quantities for studying the mechanisms of cardiac-specific viral infection. OBJECTIVE: This study examined whether human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) could be used to model the pathogenic processes of coxsackievirus-induced viral myocarditis and to screen antiviral therapeutics for efficacy. METHODS AND RESULTS: hiPSC-CMs were infected with a luciferase-expressing coxsackievirus B3 strain (CVB3-Luc). Brightfield microscopy, immunofluorescence, and calcium imaging were used to characterize virally infected hiPSC-CMs for alterations in cellular morphology and calcium handling. Viral proliferation in hiPSC-CMs was quantified using bioluminescence imaging. Antiviral compounds including interferonbeta1, ribavirin, pyrrolidine dithiocarbamate, and fluoxetine were tested for their capacity to abrogate CVB3-Luc proliferation in hiPSC-CMs in vitro. The ability of these compounds to reduce CVB3-Luc proliferation in hiPSC-CMs was consistent with reported drug effects in previous studies. Mechanistic analyses via gene expression profiling of hiPSC-CMs infected with CVB3-Luc revealed an activation of viral RNA and protein clearance pathways after interferonbeta1 treatment. CONCLUSIONS: This study demonstrates that hiPSC-CMs express the coxsackievirus and adenovirus receptor, are susceptible to coxsackievirus infection, and can be used to predict antiviral drug efficacy. Our results suggest that the hiPSC-CM/CVB3-Luc assay is a sensitive platform that can screen novel antiviral therapeutics for their effectiveness in a high-throughput fashion.

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